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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

2/14/00

MEMORANDUM

SUBJECT: **Vinclozolin.** Preliminary Human Health Risk Assessment (Chemical I.D. No. 113201, DP Barcode D245692)

FROM: William J. Hazel, Ph.D., Chemist
Reregistration Branch 1
Health Effects Division (7509C)

THROUGH: Whang Phang, Ph.D., Branch Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

TO: Deanna Scher/Susan Lewis
Reregistration Branch 1
Special Review and Reregistration Division (7508C)

Attached is the preliminary human health risk assessment for **Vinclozolin** prepared by Reregistration Branch 1 of the Health Effects Division (HED) of EPA's Office of Pesticide Programs. This document supersedes the 7/15/97 HED Chapter by incorporating: (i) the calculation of a unit risk value (Q_1^*); (ii) recent selection of a more sensitive dose and endpoint to be used in acute dietary risk assessment; (iii) assessment of the FQPA Safety Factors; (iv) cancellation of U.S. uses on stone fruits and strawberries; (v) restriction of use on turf to sod farms and golf course greens and tees; (vi) consideration of the potential residential exposure resulting from turf uses and the concomitant aggregate risk; (vii) the conduct of a new water assessment by the Environmental Fate and Effects Division (EFED); (viii) recent policies concerning the conduct of acute dietary exposure assessments; and (ix) updated figures from the Biological and Economic Analysis Division

on percent crop treated and imported. The vinclozolin team in HED is comprised of J. Dawson (occupational and residential assessment), F. Fort (dietary exposure/risk), D. Anderson and L. Mendez (toxicology), and W. Hazel (risk assessor).

Attachment: 20 pp.

cc: F. Fort (HED), J. Dawson (HED), W. Hazel (HED), L. Mendez (HED), D. Anderson (HED), D. Young (EFED), List A File, SF, RF
RDI: C. Olinger for W. Phang: 2/1/00; RARC: 2/3/00
7509C:CM2:722J:wjh:RRB1:W.J.Hazel:305-7677:2/14/00

INTRODUCTION

This preliminary human health risk assessment for vinclozolin incorporates the most recent deliberations on the hazard components of risk, use and usage information, exposure refinements, and risk assessment techniques and policies. This assessment has been conducted in accordance with current interpretations of the Food Quality Protection Act (FQPA) of August 3, 1996. Probabilistic assessment of acute dietary risks has been conducted using the DEEM^{TM} Software, up-to-date usage (percent crop imported and treated) data, the hazard endpoint and dose derived from a rat developmental toxicity study, and the recently assessed FQPA Safety Factor. Chronic dietary risks were calculated using DEEM^{TM}, recent usage data, and the FQPA factor. A nonlinear (MOE) approach was used for dietary cancer risk assessment because the available toxicity data indicate that vinclozolin is an endocrine-disrupting chemical that induces a hormonally-mediated increase in Leydig cell tumors in rats in what appears to be a threshold response. As agreement has not yet been reached regarding an appropriate Agency level of concern for cancer risk using the MOE approach, a Q_1^* unit risk figure was calculated although there is no evidence of a linear, genotoxic mode of tumor induction. Thus, a comparison of the linear (nonthreshold) and nonlinear approaches has been made to permit better informed risk management decisions. The terminal metabolite of vinclozolin, 3,5-dichloroaniline (3,5-DCA), is considered to have a genotoxic mode of tumor induction based on its similarity to p-chloroaniline, the Q_1^* of which was used in a linear cancer risk assessment; 3,5-DCA is a common metabolite of two related fungicides, iprodione and procymidone. Occupational risks were calculated to reflect the following: use of chemical-specific human exposure and residue dissipation studies, selection of the most sensitive hazard endpoint and dose for short- and intermediate-term exposure durations, and calculation of occupational cancer risk using the Q_1^* for greenhouse scenarios. It has been determined that certain turf uses may result in residential exposure thus necessitating calculation of residential postapplication risk figures. An assessment of the potential exposure to vinclozolin and its degradates through drinking water was conducted by EFED. Aggregate acute, chronic (noncancer), short-term, intermediate-term, and carcinogenic risks resulting from exposure to vinclozolin via relevant dietary (food and drinking water) and residential routes of exposure were assessed.

EXECUTIVE SUMMARY

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the vinclozolin database and conducted a preliminary human health risk assessment for vinclozolin. This assessment supersedes the 7/15/97 HED Chapter.

Vinclozolin [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione] is a dicarboximide fungicide registered in the United States for foliar use on caneberries, Belgian endive, lettuce, kiwi, and dry bulb onions. Tolerances are expressed in terms of

vinclozolin and its metabolites containing the 3,5-dichloroaniline moiety (40 CFR 180.380). A tolerance for vinclozolin residues in or on succulent beans expired 10/1/99; the Agency did not renew this tolerance. Two Section 18 Emergency Exemptions have permitted use in previous years on canola in MN and ND; however, these registrations were not approved by the Agency for the 1999 growing season. A petition (PP#0F6079) has been submitted by BASF (received 11/17/99) requesting tolerances for vinclozolin residues in or on canola and snap bean as well as Section 3 registrations for use on these crops. Tolerances have been established with no U.S. registrations to permit importation of vinclozolin-treated cucumbers, sweet peppers, and wine reflecting treatment of wine grapes. Also, tolerances currently exist for vinclozolin residues in/on stone fruits and strawberries; BASF Corporation, Agricultural Products voluntarily cancelled these uses and deleted them from their vinclozolin labels on 9/4/98 in response to the cancellation notice in the Federal Register (7/30/98). However, in accordance with the existing stocks provision, use was permitted on stone fruits and strawberries through 1/30/00. Therefore, the Agency has estimated dietary risks both including and excluding these foods from the diet.

Vinclozolin is formulated as a 50% dry flowable (DF) or 50% extruded granule (EG) in water-soluble bags (both under EPA Reg. No. 7969-85). Vinclozolin is applied using either aerial or ground equipment. Applications may be made between 7 and 30 days of harvest of food crops. Residential exposure to vinclozolin is expected as a result of the use on turf sod and golf course greens, tees, and other areas mowed to a maximum height of 1 inch.

The principal toxic effects induced by vinclozolin are related to its antiandrogenic activity and its ability to act as a competitive antagonist at the androgen receptor. There is evidence that vinclozolin binds fairly weakly to the androgen receptor but that at least two vinclozolin metabolites occurring in mammals, plants, and soil are responsible for much of the antiandrogenic activity attributable to vinclozolin.

The FQPA Safety Factor for the protection of infants and children (as required by FQPA) has been **retained (10X)** for vinclozolin. The rationale for retention of the 10X FQPA Safety Factor is: (i) there is evidence of increased susceptibility to offspring following *in utero* exposure to vinclozolin in the prenatal developmental toxicity study in rats and (ii) a developmental neurotoxicity study in rats with an expanded protocol is required for vinclozolin due to concern for the antiandrogenic properties of vinclozolin and its metabolites. Note that reproductive effects (seen in testes, sperm, epididymes, and ovaries) were observed at one or more dose levels in the chronic studies used to establish the chronic RfD. Also, the developmental neurotoxicity study could provide information relevant to all population subgroups and exposure durations.

Some of the effects induced by vinclozolin and/or its metabolites are summarized below as are the doses to be used in the various types of risk assessments:

- **Acute dietary.** The No Observed Adverse Effect Level (NOAEL), adjusted for a single dose, for acute dietary risk assessment was 6 mg/kg/day from an oral developmental rat study. Decreased ventral prostate weight in male offspring occurred at the adjusted Lowest Observed Adverse Effect Level (LOAEL) of 11.5 mg/kg/day. This effect is the most sensitive indicator of acute antiandrogenic developmental toxicity. Acute dietary risk assessment has been conducted only on females of child-bearing age because this toxicity endpoint is an *in utero* effect. Adverse effects applicable to other subpopulations and resulting from a single dose were not observed. The total uncertainty factor is assessed at 1000X (10X for interspecies extrapolation, 10X for intraspecies variation, and the 10X FQPA factor). Division of the aRfD by this total uncertainty factor results in an acute Population Adjusted Dose (aPAD) for females 13-50 of 0.006 mg/kg/day.

- **Chronic dietary.** Effects observed at the LOAEL of 2.3 mg/kg/day in rat oral chronic/carcinogenicity studies include histopathological lesions of the lungs, liver, ovaries, and eyes. The NOAEL was 1.2 mg/kg/day. As in the case of acute dietary, the total uncertainty factor is 1000X, resulting in a cPAD of 0.0012 mg/kg/day.

- **Carcinogenic dietary.** Vinclozolin is classified as a Group C carcinogen based on Leydig (interstitial testicular) cell tumors in a combined rat chronic/carcinogenicity study. A nonlinear (MOE) approach was determined to be appropriate based on a weight of the evidence conclusion that tumor induction is via an antiandrogenic mechanism. Epididymal weight decreases occurred at the LOAEL of 30 mg/kg/day; the point of departure for use in the nonlinear risk assessment is 4.9 mg/kg/day. A policy decision regarding an appropriate MOE of concern for hormonally-mediated carcinogenic effects has not yet been determined. Therefore, a Q_1^* of 2.9×10^{-1} $(mg/kg/day)^{-1}$ was calculated. The MOE and Q_1^* approaches to carcinogenic dietary risk have both been conducted to permit comparison for risk management purposes.

- **Short- and intermediate-term dermal and inhalation (females 13+).** The rat developmental study NOAEL of 3 mg/kg/day, not adjusted for a single dose, has been selected for these risk assessments (refer to acute dietary, above). The MOE of concern for females of child-bearing age is 1,000X. A dermal absorption factor of 25% has been used to calculate dermal exposure. A default inhalation absorption factor of 100% has been assumed.

- **Short- and intermediate-term dermal and inhalation (infants and children).** Delayed puberty was observed at the LOAEL of 15 mg/kg/day following postnatal dosing in a rat developmental study. The NOAEL for these risk assessments was 5 mg/kg/day. The MOE of concern is 1,000X. A dermal absorption factor of 25% has been used to calculate dermal exposure. A default inhalation absorption factor

of 100% has been assumed.

C **Long-term dermal and inhalation: cancer and noncancer.** Refer to the chronic and carcinogenic dietary sections (above) for descriptions of the relevant toxicity studies, doses, and toxic effects observed. The NOAEL of 1.2 mg/kg/day has been used for long-term dermal and inhalation noncancer risk assessment. The NOAEL of 4.9 mg/kg/day was used for the nonlinear (MOE) risk assessment approach whereas the Q_1^* of 2.9×10^{-1} $(mg/kg/day)^{-1}$ was used in a low-dose linear extrapolation. Long-term exposure is expected to result only from certain occupational greenhouse scenarios. A dermal absorption factor of 25% has been used to calculate dermal exposure. A default inhalation absorption factor of 100% has been assumed.

Also, as per a 2/14/94 HED policy, the carcinogenic potential of all chloroanilines is to be assumed to be the same as that of p-chloroaniline unless there is sufficient evidence that the chloroaniline in question is either not carcinogenic or is of a different potency than p-chloroaniline, for which a Q_1^* of 6.38×10^{-2} $(mg/kg/day)^{-1}$ has been calculated. As a result, a low-dose linear extrapolation was conducted on 3,5-DCA per se resulting solely from the use of vinclozolin. The dietary risk due to 3,5-DCA derived from vinclozolin was aggregated with 3,5-DCA risks associated with the use of two related fungicides, iprodione and procymidone which also have 3,5-DCA as a terminal metabolite.

Dietary risk assessments reflected somewhat refined exposure estimates; anticipated residues based on field trial data, percent of crop imported and/or treated figures, and use of the DEEM™ software were utilized. Refinements permit more realistic food exposure estimates for comparison of Drinking Water Levels of Comparison (DWLOCs) with estimates of potential drinking water concentrations provided by the Environmental Fate and Effects Division (EFED).

A probabilistic/Monte Carlo type of acute dietary risk assessment was conducted using an aPAD of 0.006 mg/kg/day based on an *in utero* developmental effect. Acute dietary risks to females (13-50 years), the only relevant population subgroup, were 210% of the aPAD at the 99.9th percentile of exposure if the diet is assumed to include stone fruits, strawberries, canola, succulent beans, and all other crops having vinclozolin tolerances (Table 3). Upon exclusion of stone fruits, strawberries, grapes (wine), and dry bulb onion (while retaining canola and succulent bean), acute risks fell below the Agency's level of concern (94% aRfD) at the 99.9th percentile of exposure. A sensitivity analysis was conducted in which the tail (>99.9th percentile of exposure or consumption) of the distribution were found not to contain unreasonable consumption or exposure (residue) values; grapes/wine comprised 69% of the tail and residues in wine grapes ranged from 2 to 5.8 ppm. Note that acute dietary risks were below the Agency's level of concern at the 99.5th percentile of exposure [94% aRfD for all crops and 40% aRfD excluding stone fruits, strawberry, grapes (wine), and dry bulb onions]; as the use of field trial data is

conservative, default processing factors were used, and several %CT figures used for imported crops were conservative, risks at the 99.9th percentile of exposure are conservative. Recall that adequate monitoring data are not available for vinclozolin and its regulated metabolites.

Chronic dietary risks were calculated using a cPAD of 0.0012 mg/kg/day; chronic dietary risks to all population subgroups were $\leq$14% of the cPAD. Cancer risks calculated using the nonlinear (threshold or MOE) approach were 58,000 (2.5×10^{-5} using the linear, Q_1^* approach) when all crops having vinclozolin tolerances (including stone fruits and strawberry) as well as canola and succulent bean are included in the diet. Upon exclusion of strawberry and stone fruit, the corresponding risk was an MOE of 110,000 (1.3×10^{-5}). Exclusion of strawberry and stone fruit is logical considering that these crops have been deleted from all labels and, therefore, significant residues will not occur in these crops following their most recent growing seasons; also, the toxic effects are believed to reflect chronic dietary exposure.

Also, a cancer dietary (food sources only) risk assessment using a low-dose linear extrapolation was conducted on 3,5-dicloroaniline (3,5-DCA) per se resulting solely from the use of vinclozolin. Note that 3,5-DCA is a degradate/metabolite of vinclozolin. The Q_1^* used was 6.38×10^{-2} $(mg/kg/day)^{-1}$ established for p-chloroaniline. There have been no other toxic effects/doses identified for 3,5-DCA because, not being a pesticide, this chemical does not have a toxicity data base. Cancer risks were 5.4×10^{-7} when it was assumed that strawberry, stone fruits, canola, and succulent beans as well as all other crops having vinclozolin tolerances are consumed; upon the exclusion of strawberry and stone fruits, risks declined to 2.9×10^{-7}. Neither of these risks exceed the Agency's level of concern (1×10^{-6}). Note that the risks due to 3,5-DCA from the use of vinclozolin, iprodione, and procymidone have been accumulated/aggregated (see Cumulative Exposure and Risk section).

The EFED water assessment included modeling of vinclozolin per se in groundwater and surface water as well as modeling of vinclozolin and its degradates assuming total breakdown to 3,5-DCA. This latter assumption is considered to be conservative but not unreasonable because 3,5-DCA is the terminal residue in soil/water (and, therefore, persistent) and it is mobile. Acute DWLOCs were not calculated because the risk to females 13-50 due to food sources alone exceeded the Agency's level of concern; similarly, cancer DWLOCs (Q_1^* approach) were not calculated for vinclozolin and its metabolites. As an acceptable level of concern has not been determined for cancer risk using the nonlinear (MOE) approach, DWLOCs cannot be calculated for this type of assessment.

Note that modeled vinclozolin exposure estimates due to drinking water alone (i.e., without considering food sources) do not suggest concern for adults and children from exposure to vinclozolin per se in drinking water. The cancer risk associated with 3,5-DCA in drinking

water derived from surface water, assuming total degradation of vinclozolin and its metabolites to 3,5-DCA, are potentially of concern assuming that the highest chronic EEC (3.12 ppb in surface water) level occurs in all of the water consumed. The carcinogenic DWLOC for 3,5-DCA has been calculated to be 0.25 ppb for the general population; the EEC exceeds the DWLOC by 12x indicating a potential for concern. Note, however, that this estimate is based on a model that assumes 100% degradation to 3,5-DCA and that the dietary portion of the calculation assumes a worst-case estimate of the proportion of 3,5-DCA (10% of the total radioactive residue) in plant metabolism studies. In addition, drinking water sources of 3,5-DCA derived from iprodione have been considered in the Cumulative Exposure and Risk section.

Exposure to vinclozolin in residential and other nonoccupational settings is possible as a result of occupational use on turf. Postapplication exposure to golfers following treatment of greens and tees and to toddlers resulting from vinclozolin use on sod farms may occur. These exposures are considered to be of a short-/intermediate-term duration by the Agency. Adult golfer exposures were less than the Agency's level of concern (i.e., the uncertainty factor of 1000 was easily exceeded) even on the day of application (MOE = 6800). Likewise, given the magnitude of the MOE for adults, the Agency does not believe that risks for child golfers would exceed the level of concern. The aggregate MOE for toddlers playing on sodfarm turf (which represents an upper-bound exposure that includes dermal and nondietary ingestion pathways) is 33 on the day of application. Foliar dislodgeable residues on the sod decline such that risks don't fall beneath the Agency's level of concern until 24 days after application (MOE = 1100). If 2 days are allowed for sod harvest, transit, and placement, then treated sod cannot be harvested for at least 22 days after application. As guidance becomes available and it is feasible from a regulatory perspective, this residential exposure assessment may be modified to include spray drift, residential residue track-in, exposures to farmworker children, and exposures to children in schools.

Aggregate exposure is comprised of dietary sources (both food and water) as well as residential exposure to vinclozolin. Quantitative determination of the contribution of vinclozolin in drinking water to the aggregate risk cannot be made because the EECs were generated via modeling, as opposed to actual monitoring data. HED attempts to determine the relative allowable or target contribution of drinking water to the aggregate risk by calculating DWLOCs; as noted above, the contribution of drinking water residues of vinclozolin per se to both acute and chronic aggregate risk is not expected to be significant. However, 3,5-DCA in drinking water could potentially present a cancer risk of concern based on models. Water monitoring data are not available on 3,5-DCA.

Acute aggregate risk exceeds the Agency's level of concern based on food sources of exposure alone. As a result, a DWLOC cannot be calculated. Acute dietary (food only) risks exceed the Agency's level of concern as the only applicable population, females 13-50, has a risk that is 210% of the aPAD. However, the additional contribution of drinking

water exposure to the acute aggregate risk is expected to be minimal.

Short-term and intermediate-term aggregate risks have not been calculated because the residential component exceeds the Agency's level of concern. Risk mitigation options that may need to be considered by vinclozolin stakeholders include determination of which additional crops may need to be cancelled to reduce the dietary risk and/or the duration of the PHI necessary for treated sod to reduce residential risks to toddlers below the Agency's level of concern in light of decreases in dietary risk.

Chronic (noncancer) aggregate risk was below the Agency's level of concern for food and drinking water sources of exposure. As noted above, chronic food-source risks were $\leq$14% of the cPAD. Estimated Environmental Concentrations (EECs) were compared to the chronic DWLOCs. The chronic EEC for residues of vinclozolin per se (0.53 ppb) were well below the chronic DWLOCs for water consumption by both adults (39 for the general population and 34 for females 13-50) and children (10 ppb).

Carcinogenic aggregate risk exceeded the Agency's level of concern (1×10^{-6}) as the associated risks were $1.3\text{-}2.5 \times 10^{-5}$ depending on which commodities are included in the assessment. Therefore, DWLOCs (Q_1^* approach) were not calculated for vinclozolin and its metabolites. As an acceptable level of concern has not been determined for cancer risk using the nonlinear (MOE) approach, DWLOCs cannot be calculated for this type of assessment

The dietary (food and wine only) cancer risk to the general population associated with 3,5-DCA derived from vinclozolin is estimated to be 5.4×10^{-7} (including stone fruit, strawberries, canola, and succulent beans) or 2.9×10^{-7} excluding strawberries and stone fruit. The DWLOC for 3,5-DCA originating from vinclozolin has been calculated to be 0.25 ppb for the general population; the chronic EEC of 3.12 ppb in surface water exceeds the DWLOC by 12x indicating a potential for concern.

Occupational handler exposure is expected in both the agricultural and ornamental/ floriculture marketplaces. In summary, the vast majority of occupational vinclozolin handler exposures are of a short-/intermediate-term nature and do not exceed the Agency's level of concern for virtually any of the handler exposure scenarios. Risks associated with **short-/intermediate-term occupational exposures** to handlers do not exceed the Agency's level of concern either in the agricultural or ornamental/floriculture sector regardless of the level of personal protection. **Chronic occupational handler exposure** scenarios, applicable only to very limited ornamental/floriculture uses, do not exceed the Agency's level of concern if chemical-resistant gloves are worn in addition to long pants and long-sleeved shirts.

For all occupational handler scenarios considered in the **cancer risk assessment**, MOEs at the most appropriate maximum levels of personal protection were 1400-5900 for

handheld applications and 100,000-2.9 M when water soluble packaging was used to prepare dipping solutions. Population-based cancer risk estimates for all scenarios considered were less than 1×10^{-4} (indicating that the exposure did not exceed the Agency's level of concern) and in many cases were less than 1×10^{-6}. The only scenario for which cancer risks exceeded the Agency's level of concern at all levels of personal protection considered was for backpack sprayers when used to treat cut flowers with a foliar spray.

Agricultural postapplication exposures to vinclozolin, all of which are short-/intermediate-term in duration, pose the most concern to the Agency in occupational settings. For agricultural uses, postapplication risks exceed the Agency's level of concern (i.e., an MOE <100) until 9-38 days after application. The bulk of occupational postapplication scenarios would require a Restricted Entry Interval (REI) of 21-27 days within which time residues would dissipate to concentrations below the Agency's level of concern. Note that an REI of 38 days would be required for hand harvesting of onions and trellised snapbeans; these are plausible yet fairly uncommon crop/harvesting technique combinations in agriculture.

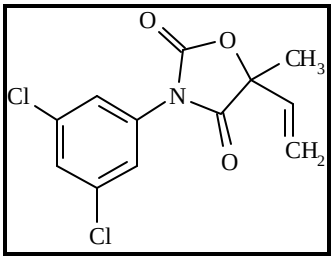
The **occupational postapplication** risks in the ornamental and floriculture sector include a short-/intermediate-term, chronic, and cancer risk assessment. **Short-/intermediate-term exposure** risks for most uses do not exceed the Agency's level of concern within 30 days after application; however, for cutting flowers in a greenhouse, 30 to 39 days were required for exposures to decrease below the Agency's level of concern. **Chronic exposures** were only considered for certain tasks associated with the production of ornamentals in a greenhouse. Durations required for entry into a previously treated area were calculated to be 31-48 days when exposures are of a chronic duration. For the **postapplication cancer risk assessment**, population-based risks exceed the Agency's level of concern ($>1 \times 10^{-4}$) even 50 days after application for all activities; durations longer than 50 days far surpass any logical proposal for establishing a viable REI. Likewise, when cancer MOE values were calculated 50 days after application, these values were all <2000 for the same scenarios.

The vinclozolin database is complete and adequate for the conduct of this human health risk assessment. However, exposure to vinclozolin *in utero* or during early development has the potential to affect the development and function of the neuroendocrine system. Consequently, a Developmental Neurotoxicity Study (DNT) is required for this chemical. The Agency acknowledges that the current DNT protocol may not be sufficient to detect the subtle findings reported in the current literature, and an expanded DNT study protocol may be necessary to assess the relevant endpoints. Data that would permit further refinement of dietary exposure include generation of monitoring data (market basket survey), a wine fermentation study to elucidate vinclozolin degradation during the fermentation process, and cooking/canning data. Data needs and labeling changes to permit refinement of occupational and residential exposure estimates will be determined during risk mitigation.

PHYSICAL/CHEMICAL PROPERTIES

Description of Chemical

Vinclozolin [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione] is a fungicide used on fruits, vegetables, and ornamentals to control various blights and rots caused by *Botrytis spp.*, *Sclerotinia spp.*, and other fungal pathogens.



Empirical Formula:	$C_{12}H_9Cl_2NO_3$
Molecular Weight:	286.11
CAS Registry No.:	50471-44-8
Chemical I.D. No.:	113201

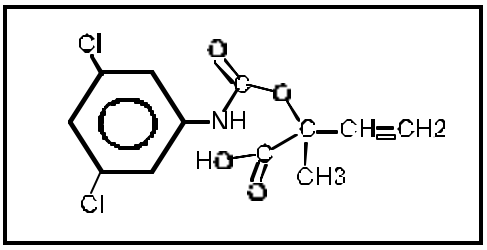
Identification of Active Ingredient

Vinclozolin is a colorless to white crystalline solid with a melting point of 108 °C. Technical vinclozolin is slightly soluble in water (<1 g/kg), and more soluble in benzene (146 g/kg), ethyl acetate (253 g/kg), chloroform (319 g/kg), and acetone (435 g/kg). Vinclozolin hydrolyzes slowly in alkaline solutions.

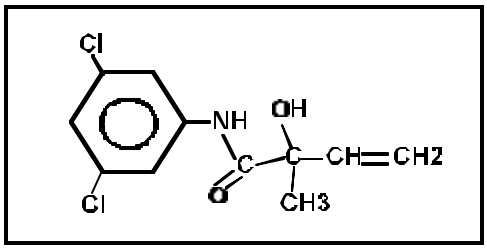
HAZARD ASSESSMENT

The toxicology database of vinclozolin has been reviewed by HED. Vinclozolin is an endocrine-disrupting chemical exerting its effects most dramatically during the developmental stages of animals ultimately resulting in reproductive effects; it also interferes with lipid metabolism and/or storage. Male fertility decrements resulting from androgen deprivation of several organs are some of the more sensitive hazard endpoints. Some effects on male fertility include reduced sperm count, decreased prostate weight, and delayed puberty. The principal toxic effects induced by vinclozolin are related to its antiandrogenic activity and its ability to act as a competitive antagonist at the androgen

receptor. Vinclozolin and/or its metabolites cause Leydig cell (testicular) tumors by a nongenotoxic mode of action. There is evidence that vinclozolin binds fairly weakly to the androgen receptor but that at least two vinclozolin metabolites occurring in mammals, plants, and soil are responsible for much of the antiandrogenic activity attributable to vinclozolin. These metabolites, known as M1 (also Metabolite B) and M2 (Metabolite E), have both undergone cleavage of the oxazolidine ring (see structures below). M1 is a reversible hydrolysis product and M2 is an irreversible
product following the loss of a Carbon atom from the oxazolidine ring. The relative androgen receptor binding affinity, determined by the ability to displace a known



M1 = Metabolite B (Ki = 97 µM)



M2 = Metabolite E (Ki = 9.7 µM)

steroidal androgen receptor binding agent in vitro, is M2>M1>Vinclozolin. Some of the effects induced by vinclozolin and/or its metabolites are summarized below.

Acute toxicity. Vinclozolin has low acute toxicity as evidenced by the Toxicity Categories of III or IV associated with oral, dermal, eye, and inhalation exposure (Table 1). It does, however, act as a dermal sensitizer. The No Observed Adverse Effect Level (NOAEL) for acute dietary risk assessment was 3.1 mg/kg/day from an oral developmental rat study in which decreased ventral prostate weight in male offspring occurred at the Lowest Observed Adverse Effect Level (LOAEL) of 6.3 mg/kg/day. These study doses were then adjusted to derive the single dose causing this acute effect by multiplying by the plasma equilibrium factor of 1.84 resulting in adjusted doses of 6 mg/kg/day (NOAEL) and 11.5 mg/kg/day (LOAEL). Adjustment was necessary because the developmental effects are expected to result from a single day (or less) of exposure; the peak effect occurred on gestation day 19. However, the internal dose of 6 mg/kg could not be achieved in rats receiving a single oral dose of 6 mg/kg. This factor was determined from a rat metabolism study by comparing the plasma concentration of vinclozolin 2 hours after one dose to that 2 hours after the last of seven daily doses, at which time equilibrium had been attained. Other developmental effects that are likely to be antiandrogenic effects were observed at higher doses and include decreased anogenital distance, increased incidence of areola formation and nipple development in male offspring, reduced viable sperm count, and reduced fertility. As these effects were observed to have been initiated via *in utero* exposure during fetal development, acute dietary risk assessment has been conducted only on females (13 years and older), i.e., females of child-bearing age. No toxicological effects applicable to other populations and attributable to a single dose were observed.

The uncertainty factors (UF) due to intraspecies variability (10X) and interspecies extrapolation (10X) result in a total hazard-based UF of 100X: the acute Reference Dose (aRfD) is thus 6 mg/kg/day/100 = 0.06 mg/kg/day. Since the FQPA factor of 10X was retained, the acute Population Adjusted Dose (aPAD) used for acute dietary risk assessment is 0.006 mg/kg.day.

Chronic dietary. Effects observed at the LOAEL of 2.3 mg/kg/day in rat oral chronic/carcinogenicity studies include histopathological lesions of the lungs (foam cell aggregates in males), liver (eosinophilic foci in males), ovaries (interstitial cell lipidosis in females), and eyes (lenticular degeneration in both sexes). At higher dose levels, reproductive effects on the testes, sperm, epididymes, and ovaries occurred. The NOAEL was 1.2 mg/kg/day. The UF due to intraspecies variability (10X) and interspecies extrapolation (10X) results in a total hazard-based UF of 100X: the chronic RfD is thus 1.2 mg/kg/day/100 = 0.012 mg/kg/day. Since the FQPA factor of 10X was retained, the chronic Population Adjusted Dose (cPAD) used for chronic dietary risk assessment is 0.0012 mg/kg.day.

Carcinogenic dietary. Vinclozolin is classified as a Group C carcinogen, i.e., a possible human carcinogen via relevant routes of exposure. The basis was a statistically significant increase in Leydig (interstitial testicular) cell tumors observed in combined chronic and carcinogenic Wistar rat studies. A nonlinear (MOE) approach to risk quantification was determined to be appropriate due to the evidence of tumor induction by an antiandrogenic mechanism as opposed to a direct genotoxic mode of action. Epididymal weight decreases were observed in both generations of the rat reproduction study at the LOAEL of 30 mg/kg/day; the point of departure selected for the nonlinear cancer risk assessment was 4.9 mg/kg/day. A policy decision regarding an appropriate MOE of regulatory concern for hormonally-mediated carcinogenic effects has not yet been made. Therefore, a default Q_1^* has been calculated to be 2.9×10^{-1} $(mg/kg/day)^{-1}$ based on Leydig cell tumors in a Wistar rat chronic toxicity/carcinogenicity study. It is noted that Vinclozolin was clearly nonmutagenic in five of six mutagenicity studies. In a single *in vitro* study, there was uncertain evidence of the mutagenicity of vinclozolin as mutation frequency increased only upon activation and only at vinclozolin concentrations that were cytotoxic and apparently above the solubility of vinclozolin. Both the MOE and Q_1^* approaches have been used to calculate carcinogenic dietary risk to the general U.S. population.

Short- and intermediate-term dermal and inhalation (females 13+). The rat developmental study NOAEL of 3 mg/kg/day, not adjusted by the plasma equilibrium factor, has been selected for these risk assessments (refer to acute dietary, above). The MOE of concern is 1,000X attributable to intraspecies variability (10X), interspecies extrapolation (10X), and FQPA Safety Factor (10X). A dermal absorption factor of 25%, based on a rat dermal absorption study, has been used to calculate dermal exposure. A default inhalation absorption factor of 100% has been assumed.

Short- and intermediate-term dermal and inhalation (infants and children). Delayed puberty, as measured by preputial separation, was observed at the LOAEL of 15 mg/kg/day in a rat developmental study following oral dosing with vinclozolin from weaning to 15 weeks of age. The NOAEL of 5 mg/kg/day has been selected for these risk assessments. The MOE of concern is 1,000X due to intraspecies variability (10X), interspecies extrapolation (10X), and FQPA Safety Factor (10X). A dermal absorption factor of 25% has been used to calculate dermal exposure. A default inhalation absorption factor of 100% has been assumed. As delayed puberty was likely to have been a vinclozolin-induced effect resulting from androgen deprivation during the growth and development stages, this endpoint is applicable only to infants and children

Long-term dermal and inhalation: cancer and noncancer. Refer to the chronic and carcinogenic dietary sections (above) for descriptions of the relevant toxicity studies, doses, and toxic effects observed. The oral NOAEL of 1.2 mg/kg/day has been used for long-term dermal and inhalation noncancer risk assessment. The point of departure of 4.9 mg/kg/day was used for the nonlinear (MOE) carcinogenic risk assessment approach whereas the Q_1^* of 2.9×10^{-1} $(mg/kg/day)^{-1}$ was used in a low-dose linear extrapolation model to carcinogenic risk assessment. Long-term exposure is expected to result only from certain occupational greenhouse scenarios. A dermal absorption factor of 25% has been used to calculate dermal exposure. A default inhalation absorption factor of 100% has been assumed.

Following oral administration of radiolabeled material, vinclozolin is rapidly and extensively absorbed into the rat gastrointestinal tract, metabolized, and the parent compound and metabolites are rapidly excreted. About 80% of the administered dose is excreted within 2 days and 98% within 5 days with roughly equal amounts being excreted in the urine and feces. No radioactivity was excreted as CO_2 or other respired compounds. There is no evidence of bioaccumulation. The predominant radiolabeled compound found in the urine was a glucuronide conjugate of a trihydroxybutyramide, M1, and M2 (see structures above). In feces, the major products excreted were the trihydroxybutyramide and vinclozolin per se. Less than 1% of the administered dose was hydrolyzed to 3,5-DCA although the majority of the residues contained the 3,5-DCA moiety; this is a requirement for inclusion in the tolerance expression (see 40 CFR 180.380) and as a residue of toxicological concern.

Also, as per a 2/14/94 HED policy, the carcinogenic potential of all chloroanilines will be assumed to be the same as that of p-chloroaniline (PCA) unless there is sufficient evidence that the chloroaniline in question is either not carcinogenic or is of a different potency than PCA. The Q_1^* of PCA has been calculated to be 6.38×10^{-2} $(mg/kg/day)^{-1}$ based on the spleen sarcoma rate in male rats from an NTP bioassay (Fisher, 1994). As a result, a dietary low-dose linear extrapolation was conducted on 3,5-DCA per se, the terminal metabolite of vinclozolin in plants, animals, and soil. Note that two related dicarboximide fungicides, iprodione and procymidone, also contain the 3,5-DCA moiety

and potentially have 3,5-DCA as a terminal metabolite.

For details of the vinclozolin hazard assessment, refer to the Vinclozolin Toxicology Chapter of the Reregistration Eligibility Decision by D. Anderson as updated by the 12/8/99 HIARC report (see below)

DOSE RESPONSE AND HAZARD ENDPOINT SLECTION

A summary of the vinclozolin toxicology studies and hazard dose and endpoint selections made by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) is provided in the HIARC report by D. Anderson dated 12/8/99. Table 1 contains the acute toxicity endpoints which are especially important for labeling purposes, eg. for label warnings and the level of personal protective equipment (PPE) necessary for vinclozolin handlers. Table 2 contains a summary of the hazard doses and endpoints selected for use in the various human health risk assessments.

FQPA Safety Factor

The FQPA Safety Factor Committee met 11/22/99 to evaluate the hazard and exposure data for vinclozolin as bases for making a recommendation on the magnitude of the FQPA Safety Factor for the protection of infants and children (as required by FQPA). The Committee recommended that the FQPA safety factor be **retained (10X)** for vinclozolin. The rationale for retention of the 10X FQPA Safety Factor is explained in the Committee's 12/15/99 report, excerpted as follows:

i. There is evidence of increased susceptibility to offspring following *in utero* exposure to vinclozolin in the prenatal developmental toxicity study in rats; and
ii. A developmental neurotoxicity study in rats with an expanded protocol is required for vinclozolin due to concern for the antiandrogenic properties of vinclozolin and its metabolites.

The Committee recommended that the 10X safety factor be applied to Females 13-50 when assessing acute dietary risk. As a result, the acute Population Adjusted Dose (aPAD) for females 13-50 is aRfD/10 or 0.06 mg/kg/day/10 = 0.006 mg/kg/day. No appropriate dose/endpoint was identified by the HIARC for use in acute dietary risk assessments for Infants and Children. When assessing short-term/intermediate-term residential (non-occupational) exposures, the 10X safety factor is applicable to both Females 13-50 and Infants and Children subpopulations since an increase in susceptibility of offspring was observed following *in utero* exposure of rats in the developmental study (which could potentially occur after a single dose) as well as upon postnatal exposure of rat

offspring.

The Committee also recommended that the 10X safety factor be applied to all population subgroups when assessing chronic dietary exposures since there is concern for reproductive effects (seen in testes, sperm, epididymes, and ovaries) observed at one or more dose levels in the chronic studies used to establish the chronic RfD. Additionally, there is a data gap for the developmental neurotoxicity study which could provide information relevant to all population subgroups and exposure durations. As a result, the chronic PAD (cPAD) for all population subgroups is cRfD/10 or 0.012 mg/kg/day/10 = 0.0012 mg/kg/day.

DIETARY EXPOSURE AND RISK ASSESSMENT

Food Sources of Dietary Exposure

Tolerances are established for the combined residues of vinclozolin and its metabolites containing the 3,5-dichloroaniline moiety in or on plant commodities [40 CFR §180.380]. Adequate data collection and enforcement methods are available to detect vinclozolin residues in plant commodities. Vinclozolin is registered in the United States for foliar use on caneberries, Belgian endive, lettuce, kiwi, and dry bulb onions. A tolerance for vinclozolin residues in or on succulent beans expired 10/1/99; the Agency did not renew this tolerance. Two Section 18 Emergency Exemptions have permitted use on canola in MN and ND; however, these registrations were not approved by the Agency for the 1999 growing season. A petition (PP#0F6079) has been submitted by BASF (received 11/17/99) requesting tolerances for vinclozolin residues in or on canola and snap bean as well as Section 3 registrations for use on these crops. Tolerances have been established with no U.S. registrations to permit importation of vinclozolin-treated cucumbers, sweet peppers, and wine reflecting treatment of wine grapes. Also, tolerances currently exist for vinclozolin residues in/on stone fruits and strawberries; however, BASF Corporation, Agricultural Products has voluntarily cancelled these uses and deleted them from their vinclozolin labels. No meat, milk, poultry, or egg tolerances have been established for vinclozolin residues because there are no feed items derived from crops on which vinclozolin is currently registered. However, use on canola, if approved, would necessitate reconsideration of the need for tolerances in livestock commodities. Due to the repeated Section 18 exemptions for vinclozolin use on canola

Table 1. Acute toxicity studies on vinclozolin.

Test	Result	Toxicity Category
Acute Oral LD50 in Rats MRID# 00080451 & 92194010, Study# BASF XXII/337, 90/6515, Date 2/20/73.	LD50 > 10,000 mg/kg in both males and females. Acceptable	IV
Acute Dermal LD50 Rats MRID# 00086339 & 921934011, Study# BASF 90/6516, Date 11/2/77.	LD50 > 2500 mg/kg in both males and females. Acceptable	III
Acute Inhalation LC50 in rats MRID# 00075474 & 92194012, Study# 90/6517, Date 4/20/79.	LC50 > 29.1 mg/l. Acceptable	IV
Primary Eye Irritation in Rabbits MRID# 00086341 & 92194013, Study# BASF 90/6518, Date 11/9/77	Slight eye irritation cleared by day 8. Acceptable	III
Primary Skin Irritation in Rabbits MRID# 00086340 & 92194014, Study# BASF 90/6519, Date 11/9/77.	Slight skin irritation cleared within 72 hours. Acceptable	IV
Skin Sensitization in Guinea Pigs MRID# 00080451 & 92194015, Study# BASF 90/6520, Date 9/7/79.	Skin sensitizer in 4/9 animals. Acceptable	Sensitizer

Table 2. Summary of Toxicology Endpoint Selection

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Females 13+)	Adjusted Developmental NOAEL=6 UF = 100 (10 x 10) FQPA SF = 10	Decreased ventral prostate weights at the adjusted LOAEL of 11.5 mg/kg/day.	Developmental- Rat
	Acute RfD = 0.06 mg/kg/day; Acute PAD = 0.006 mg/kg/day		
Acute Dietary (Adult Males, Infants, & Children)	No appropriate endpoint was identified in oral toxicity studies including the developmental and reproductive toxicity studies in rats and rabbits for risk assessment for populations other than Females 13+.		
Chronic Dietary	NOAEL=1.2 UF = 100 (10 x 10) FQPA SF = 10	Histopathological lesions in the lungs (males), liver (males), ovaries (females) and eyes (both sexes) at the LOAEL of 2.3 mg/kg/day.	Combined Chronic Toxicity/Carcinogenicity-Rat
	Chronic RfD = 0.012 mg/kg/day; chronic PAD = 0.0012 mg/kg/day		
Carcinogenic Dietary	Point of Departure = 4.9	Vinclozolin is classified as a Group C carcinogen with a nonlinear (MOE) approach. Epididymal weight decrements occurrred at the LOAEL of 30 mg/kg/day.	2-Generation Reproduction-Rat
Carcinogenic Dietary	$Q_1^* = 2.9 \times 10^{-1}$ $(mg/kg/day)^{-1}$	Vinclozolin is classified as a Group C carcinogen for testicular Leydig cell tumors with a Q_1^* of 2.9×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents.	Combined Chronic Toxicity/Carcinogenicity-Rat
Carcinogenic dietary risk should be calculated by two approaches: (1) the MOE, and (2) the Q_1^* approach			

Short- & Intermediate Term (Dermal and inhalation) [a] Females 13 +	Oral NOAEL=3	Decreased ventral prostate weights at the LOAEL of 6 mg/kg/day	Developmental -Rat
Short- & Intermediate Term (Dermal and inhalation) [a] Infants & Children	Oral NOAEL = 5	Increased incidence of delayed puberty at the LOAEL of 15 mg/kg/day	Developmental -Rat
Long-Term (Dermal and inhalation) [a] **Non-Cancer**	Oral NOAEL = 1.2	Histopathological lesions in the lungs (males), liver (males), ovaries (females) and eyes (both sexes)	Combined Chronic Toxicity/Carcinogenicity-Rat
Long-Term (Dermal and inhalation) [a] **Cancer**	Oral point of departure = 4.9 mg/kg/day and $Q_1^* = 2.9 \times 10^{-1}$ $(mg/kg/day)^{-1}$	Classified as a **Group C carcinogen** with a **non-linear (MOE) approach.** Also, use the Q_1^* in a low-dose linear extrapolation for human risk assessment where appropriate. These cancer risk assessments are required only for chronic exposure scenarios.	
Carcinogenic Dietary for **3,5-DCA**	$Q_1^* = 6.38 \times 10^{-2}$ $(mg/kg/day)^{-1}$	The Q_1^* is that of p-chloroaniline (PCA), assumed by HED to be representative of all chloroanilines. The PCA Q_1^* is based on the spleen sarcoma rate in male rats in an NTP study (Fisher, 1994). A low-dose linear extrapolation is to be conducted when appropriate.	

a = Appropriate route-to-route extrapolation should be performed for these risk assessments (i.e., the dermal inhalation exposure components using the appropriate absorption rates (25% for dermal and 100% for inhalation) should be converted to equivalent oral doses and compared to the oral NOAEL.

establishment on this crop, all dietary risk assessments have included not only canola but anticipated residues of vinclozolin in livestock commodities resulting from feeding canola.

Vinclozolin is formulated as a 50% dry flowable (DF) or 50% extruded granule (EG) in water-soluble bags (both under EPA Reg. No. 7969-85). Vinclozolin is applied foliarly using either aerial or ground equipment. Three to five applications are typically made between 3 and 28 days of harvest.

FDA and USDA/Pesticide Data Program monitoring data are available for most foods expected to bear vinclozolin residues. However, these monitoring data are not useful for risk assessment purposes because these programs do not analyze all 3,5-DCA-containing metabolites, which are the residues of concern. BASF, in December of 1999, submitted previously unreviewed grape and lettuce metabolism studies and a proposal that monitoring data be used as a source of refined dietary exposure estimates, i.e., anticipated residues (ARs; D261894, W. Hazel, in review). BASF proposes that, based upon these and other metabolism studies, a factor of 1.5 should be used to multiply the vinclozolin residue levels in the monitoring data to correct for levels of other 3,5-DCA-containing residues not determined by PDP or FDA. Agency review of available plant metabolism studies reveals that a significant portion of the vinclozolin residue may exist as 3,5-DCA per se or conjugates, all of which tend to increase with time as they are the terminal, more stable residues. Conjugates and 3,5-DCA per se are not analyzed by either FDA or PDP. These residues are, however, analyzed by the data collection method used to generate the field trial data because the method converts all of these residues to a common moiety (derivatized 3,5-DCA) via an alkaline hydrolysis step prior to any extraction step. There is also significant variability in the ratios of vinclozolin per se to total residues with time, between crops, and between studies on the same crop. Although a detailed review will follow, the Agency does not feel that the recently-submitted plant metabolism studies provide additional information supporting use of monitoring data to generate ARs. **As a result, field trial data have been used to calculate AR values for dietary exposure refinement purposes.** The ARs thus calculated are considered to be somewhat refined. The Agency has a high degree of confidence that these AR values will not underestimate dietary exposures although they may be considered to be conservative because they are based upon field trial data, default processing factors, and several conservative %CT figures for imported commodities. While monitoring data were not directly useful for exposure refinement, they do qualitatively support the results of the dietary exposure analyses conducted using field trial data. Note that ARs to refine the dietary (food) exposure to 3,5-DCA were assumed to be 10% of the total 3,5-DCA-containing residue derived from field trials; the 10% figure is considered to be fairly conservative as it represents the highest percentage of the total radioactive residue containing the 3,5-DCA moiety from any plant species tested in the plant metabolism studies.

OPP's Biological and Economic Analysis Division (BEAD) provided information (I. Yusef,

9/11/98 and S. Nako, 11/3/99) on the percent of domestic crop treated (%CT), the percent of imported crop treated, and, for crops having no vinclozolin U.S. registration, the percent of crop available for U.S. consumption that is imported. For the chronic analyses, the weighted average %CT was incorporated; for the acute analyses, the estimated maximum %CT was used when appropriate. Percent crop treated data for stone fruits and strawberries were obtained from the Quantitative Usage Analysis(QUA) from 9/98. These data were not provided in the latest QUA because the registrations for use on these commodities have been voluntarily canceled and the sites deleted from labels.

In acute analyses (except canola oil) the adjustment for %CT is incorporated into the residue distribution files (RDFs) via addition of zero residue values corresponding to the % crop not treated. In the chronic analyses as well as the acute AR for canola oil (the only blended commodity), the %CT is incorporated into the average residue value.

Detailed information regarding how the ARs were calculated can be found in the F. Fort memorandum dated 2/9/00 (D261993). The information was presented to HED's Chemistry Science Advisory Council on 1/12/00. The details of the DEEM^{TM} analyses can be found in the F. Fort memorandum dated 2/9/00 (D263049). This information was presented to HED's Dietary Exposure Science Advisory Council on 1/13/00. For the probabilistic acute dietary exposure analyses, the entire distribution of field trial data was used to generate residue distribution files (RDFs) for commodities that are considered to be not blended or partially blended. Canola oil is the only commodity that is considered to be blended in these analyses; the average field trial residue incorporating the likely maximum percent crop treated was used as a point estimate in this case. Chronic ARs were also calculated by averaging the applicable field trial data. No processing factors were available; therefore, the DEEM^{TM} default concentration factors were used in the dietary exposure analyses.

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For chronic dietary risk assessments, the three-day average of consumption for each subpopulation is combined with residues in commodities to determine average exposure in mg/kg/day. For refined acute dietary risk assessments, the entire distribution of consumption events for individuals is multiplied by a distribution of residues to obtain a distribution of exposures in mg/kg/day. This is a probabilistic analysis, referred to as "Monte Carlo", and the risk is reported at the 99.9th percentile of exposure.

High consumption food items for infants and children include strawberries and stone fruit. However, BASF voluntarily cancelled these uses and deleted them from their vinclozolin labels on 9/4/98 in response to the cancellation notice in the Federal Register (7/30/98). However, in accordance with the existing stocks provision, use was permitted on stone fruits and strawberries through 1/30/00. In the near term, however, these commodities are

still likely to bear vinclozolin residues. Therefore, the Agency has estimated dietary risks both including and excluding these foods from the diet. Tolerance revocation proceedings have been initiated by the Agency. New uses have been proposed in the U.S. for canola (also imported from Canada) and snap beans; dietary risk has also been estimated both including and excluding these commodities. Codex MRLs have been established for many commodities and are similar or identical to U.S. tolerances.

Acute dietary. Estimated acute dietary risk at the 99.9th percentile of exposure is above HED's level of concern for vinclozolin; this risk is to females 13-50, the only relevant population subgroup considering that the toxicological effect appropriate to this duration and route of exposure results from *in utero* exposure of offspring. This risk is 210% of the aPAD when stone fruits and strawberries are assumed to bear vinclozolin residues and canola and succulent beans are included in the diet (Table 3).

Additional analyses conducted to further characterize vinclozolin acute dietary risk indicate that imported wine, resulting from the treatment of wine grapes outside the U.S., is the most significant contributor to estimated risk. When strawberry, stone fruits, and grapes (wine) are excluded from the analysis, acute dietary risk to women 13-50 at the 99.9th percentile of exposure decreases to 110% of the aPAD; of the reduction to the aPAD, about 60% is due to wine, 40% is due to strawberries, and none is due to stone fruits. When dry bulb onions are excluded from the assessment as well as wine, strawberry, and stone fruits (the latter two are already deleted from vinclozolin labels), the risk is reduced to 94% of the aRfD, which is below the Agency's level of concern (Table 3). Note that canola and succulent beans do not appear to be significant contributors to the acute dietary risk.

The Agency conducted sensitivity analyses and determined which commodities comprised the tail (>99.9th percentile of exposure) of the acute dietary (Monte Carlo) assessment. Information was gathered from the Critical Exposure Contribution (CEC) analysis. For Females 13-50 years old, 5711 records were reviewed. Additional information was also gathered to characterize the results of the acute assessment as per the Agency's draft 99.9th percentile policy paper.

Wine grapes comprised 69% of the upper tail of the exposure and have been determined to be a significant contributor to the risk. Review of the CEC analysis showed that consumption of wine by females 13-50 years old ranged from 4 to 32 ounces of wine per day. These consumption amounts do not appear to be unreasonable. Comparison of exposure and consumption estimates using the 1989-91 and 1994-96 data showed no quantitative differences which further confirms that consumption values are not inordinate. Wine grape residue values found in the CEC ranged from 2 to 5.8 ppm indicating that the exposure was not driven by one high-end residue value. Other components of the upper tail include bulb onion (12%), kiwi (11%), leaf lettuce (4%), raspberries (3%), and succulent beans (<1%).

Table 3 also presents exposure and risk to Females 13-50 at the 99.5th and the 99th percentile of exposure for comparative purposes. Risks at the 99.9th percentile of exposure are typically used for risk assessment when the exposure figures are highly refined. In this case, the exposure assessment is considered to be only somewhat refined as it represents the use of the full distribution of relevant **field trial data** (mean for the blended canola oil), some %CT figures were unavailable for imports and were assumed to be 100%, and %CT data for canola and succulent beans are excessively high due to the low confidence in the estimates made well in advance of pending Section 3 registrations. Note that acute dietary risks were below the Agency's level of concern at the 99.5th percentile of exposure [94% aRfD for all crops and 40% aRfD excluding stone fruits, strawberry, grapes (wine), and dry bulb onions]; as the use of field trial data is conservative, default processing factors were used, and several %CT figures used for imported crops were conservative, risks at the 99.9th percentile of exposure are conservative. Recall that adequate monitoring data are not available for vinclozolin and its regulated metabolites. Further refinement would be possible if market basket survey data (including single-serving size samples, where appropriate), washing/cooking data, and additional %CT data were available.

Chronic dietary. Estimated chronic dietary exposure and risk for vinclozolin are significantly below HED's level of concern. Exposure to the general U.S. population corresponds to 7% of the cPAD whereas the most highly exposed population subgroup is children 1-6 years of age, with an estimated exposure corresponding to 14% of the cPAD; these risk figures assume that the diet includes strawberry, stone fruit, canola, and succulent bean as well as all other commodities having vinclozolin tolerances (Table 4). When strawberry and stone fruits are deleted from the chronic assessment, the most exposed subgroup is Children 1-6 with 7% of the cPAD consumed.

Carcinogenic dietary. The two types of cancer assessments conducted on the General U.S. Population are presented in Table 4. Inclusion of strawberry, stone fruit, canola, and succulent bean as well as all other commodities having vinclozolin tolerances in the chronic dietary exposure results in an estimated cancer risk of 2.5×10^{-5} using the low-dose linear extrapolation (Q_1^*) approach whereas the nonlinear (MOE) approach results in an MOE of 58,000. Upon removal of strawberry and stone fruit from the diet, cancer risk is reduced approximately two-fold (Table 4). The major contributors to the carcinogenic dietary risk are strawberries and succulent beans. Recall that the Agency has determined that the weight of the scientific evidence leads to the conclusion that the mechanism of tumor induction by vinclozolin and its metabolites is via antiandrogenic activity as opposed to a genotoxic mode of action.

Table 3. Results of the Acute Dietary Analyses for Females 13-50 years old.

Scenario	**99.9th %ile**		**99.5th %ile**		**99th %ile**	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
All	0.012964	210	0.005619	94	0.003440	57
No Stone Fruit	0.012822	210	0.005468	91	0.003302	55
No Strawberry	0.010407	170	0.003681	61	0.002273	38
No Strawberry or Stone fruit	0.010250	170	0.003417	57	0.002090	35
No Succulent beans	0.013010	220	0.005442	91	0.002988	50
No Canola	0.013303	220	0.005858	98	0.003694	62
No strawberry, stone fruit, canola or succulent bean	0.010480	180	0.002755	46	0.001122	19
No strawberry, stone fruit, or grapes	0.006400	110	0.002807	47	0.001811	30
No strawberry, stone fruit, grapes or onions	0.005637	94	0.002372	40	0.001484	25

Therefore, HED has included the linear approach to cancer risk assessment for risk management purposes awaiting the determination of an appropriate level of concern for cancer risk assessments when a nonlinear (MOE) approach is deemed applicable due to a homonally-mediated mode of carcinogenicity.

Also, as per a 2/14/94 HED policy, the carcinogenic potential of all chloroanilines is to be assumed to be the same as that of p-chloroaniline unless there is sufficient evidence that the chloroaniline in question is either not carcinogenic or is of a different potency than p-chloroaniline. The p-chloroaniline Q_1^* has been calculated to be 6.38×10^{-2} $(mg/kg/day)^{-1}$ based on the spleen sarcoma rate in male rats from an NTP bioassay (Fisher, 1994). As a result, a dietary low-dose linear extrapolation was conducted on 3,5-DCA per se resulting solely from the use of vinclozolin. Based on the worst-case estimate from plant metabolism studies that 10% of the total radioactive residues is comprised of 3,5-DCA, the Agency assumed that 10% of the total chronic dietary exposure based on field trials would consist of 3,5-DCA. Recall that the analytical method used to generate the field trial data includes an alkaline hydrolysis step that converts all 3,5-DCA-containing residues into 3,5-DCA. Cancer risks were 5.43×10^{-7} when it was assumed that strawberry, stone fruits, canola, and succulent beans as well as all other crops having vinclozolin tolerances are consumed; upon the exclusion of strawberry and stone fruits, risks declined to 2.9×10^{-7}. Neither of these risks exceed the Agency's level of concern (1×10^{-6}). The cumulative aggregated risk associated with combined human exposure to 3,5-DCA derived from vinclozolin, iprodione, and procymidone is presented in the Cumulative Exposure and Risk section.

The chronic/cancer and acute analyses do not take into consideration the potential for reduction of vinclozolin residues in cooked/canned/processed commodities, since there are no chemical-specific cooking studies. Note that 3,5-DCA per se may increase in concentration under some conditions. HED will refine the vinclozolin dietary exposure analyses if such data become available.

Drinking Water Sources of Dietary Exposure

EFED has performed modeling of parent vinclozolin and its primary metabolites of toxicological concern (M1 or B, M2 or E, and D or 3,5-DCA) in surface water and groundwater (D. Young, 12/17/99 and 2/00). EFED has considered recent data on the abiotic hydrolysis, photolysis, and metabolism of parent vinclozolin and the above compounds in the standard index reservoir. In general, available monitoring data are of limited use because the metabolite concentration measurements were not performed. For both surface water and groundwater, the sum of vinclozolin and its principal metabolites, assumed to degrade completely to 3,5-DCA, have been used to assess the cancer risk associated with 3,5-DCA whereas vinclozolin per se has been used for the vinclozolin risk assessments. Thus the 3,5-DCA EECs may be somewhat exaggerated, particularly in

Table 4. Results of the Vinclozolin Chronic and Cancer Dietary Analyses.

Scenario	Chronic										Cancer	
	Gen. Population		**All Infants**		**Children 1 - 6**		**Children 7 - 12**		**Females 13 - 50**			
	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD	Q_1*	MOE
All	0.000085	7	0.000096	8	0.000167	14	0.000100	8	0.000076	6	2.5×10^{-5}	58000
No Stone Fruit	0.000079	7	0.000065	5	0.000153	13	0.00092	8	0.000073	6	2.3×10^{-5}	62000
No Strawberry	0.000051	4	0.00095	8	0.000093	8	0.000055	5	0.000045	4	1.5×10^{-5}	95000
No Strawberry or Stone fruit	0.000046	4	0.000064	5	0.000078	7	0.000046	4	0.000041	3	1.3×10^{-5}	110000
No Succulent beans	0.000061	5	0.000049	4	0.000108	9	0.000071	6	0.000059	5	1.8×10^{-5}	81000
No Canola	0.000082	7	0.000094	8	0.000161	13	0.000096	8	0.000074	6	2.4×10^{-5}	60000
No strawberry, stone fruit, canola or succulent beans	0.000018	2	0.000016	1	0.000013	1	0.000012	1	0.000021	2	5.3×10^{-6}	270000

surface water soon after treatment (i.e., acute concentration). The use of the EECs for 3,5-DCA (Table 5) provides reasonable estimates for total vinclozolin residue DWLOCs (when all residues are expressed as DCA equivalents) but may be conservative for the EEC for 3,5-DCA per se. Onions grown in California were considered to be the worst-case scenario for water modeling.

Groundwater

The SCI-GROW model (Screening Concentrations in Ground Water) is a model for estimating "upper bound" concentrations of pesticides in ground water. SCI-GROW provides a screening concentration which is an estimate of likely ground water concentrations if the pesticide is used at the maximum allowed label rate in areas with ground water vulnerable to contamination. In most cases, a majority of the pesticide use area will have ground water that is less vulnerable to contamination than the areas used to derive the SCI-GROW estimate.

The SCI-GROW model is based on scaled ground water concentrations from ground water monitoring studies, environmental fate properties (aerobic soil half-lives and organic carbon partitioning coefficients-Koc's) and application rates. The SCI-GROW model does not make use of information on application procedures. As with the surface water modeling, 3,5-DCA was used as a surrogate for all vinclozolin residues. Refer to Table 5 for vinclozolin groundwater EECs for dietary risk assessment purposes.

Surface Water

Tier II surface water EECs were generated using PRZM 3.12 and EXAMS 2.975 using decline of parent vinclozolin and formation and decline of metabolites B, D, and E in a sequential degradation pattern in both the field and the pond such that degradation proceeds completely to Metabolite D (3,5-DCA). EECs are presented in Table 5 for total parent as well as 3,5-DCA, which reflects the combined residue following complete degradation to 3,5-DCA. Vinclozolin per se is a major residue near application but eventually the metabolites are the principal residues in both surface and drinking water. The metabolites are the only residues that are likely to be found in the environment except fairly soon after application. The scenario modeled involved application to onions in California. A Tier II EEC for a particular crop or use is based on a single site that represents a high exposure scenario for the crop or use. Weather and agricultural practices are simulated at the site for 36 years to estimate the probability of exceeding a given concentration (maximum concentration or average concentration) in a single year. Maximum EECs are calculated so that there is a 10% probability that the maximum concentration in a given year will exceed the EEC at the site; peak and chronic EECs were calculated so that there is a 10% probability that the maximum average concentration for a given duration (4-day, 21-day, etc.) will equal or exceed the EEC at the site. This can also be expressed as an expectation that water concentrations will exceed EECs once every 10 years. EECs are presented in Table 5.

Drinking Water Levels of Comparison

Drinking Water Levels of Comparison (DWLOCs) represent the maximum contribution to the human diet that may be attributed to residues of a pesticide in drinking water after dietary exposure is subtracted from the aPAD or cPAD. Acute and cancer (Q_1^*) DWLOCs could not be calculated for vinclozolin because risks due solely to food sources exceeded the Agency's respective levels of concern.

Table 5. EECs of Vinclozolin + Metabolites in Surface Water and Groundwater to be Used for Comparison to Acute and Chronic Risk DWLOCs.

Onion/California Scenario	Groundwater EECs: Acute and Chronic (ug/L)	Surface Water EECs (ug/L)*	
		Acute (peak)	Chronic (annual mean)
Vinclozolin per se	0.53	5.68	0.165
Vinclozolin + metabolites assumed to degrade completely to 3,5-DCA	2.65	26	3.12

Acute DWLOCs

Acute DWLOCs could not be calculated because the risk associated with food sources of acute dietary risk exceed the Agency's level of concern. However, if only drinking water is considered, i.e., if it is assumed that all of the water consumed per day contains vinclozolin residues at the peak surface water EEC level, the %aPAD consumed would be minimal (females 13-50). If the total residue expressed as 3,5-DCA is assumed (see Table 5), then the percent of the aPAD consumed would still be much less than 100% aPAD. Monitoring data could permit refinement of vinclozolin exposure through drinking water but it appears that food sources of dietary risk are the more significant contributors.

Chronic DWLOCs

The following chronic DWLOCs were calculated for vinclozolin using anticipated residues in food as follows: general U.S. population, 39 ppb; females 13-50, 34 ppb, and children 1-6, 10 ppb. Comparisons between DWLOCs and the highest EEC (in ground water) of 0.53 ppb for vinclozolin per se clearly indicates a lack of chronic dietary risk concern for drinking water sources of vinclozolin per se. Even comparing the 2.65 ppb ground water EEC for combined vinclozolin residues (assuming complete degradation to 3,5-DCA) indicates a lack of concern. No refinement of the chronic drinking water estimates is needed.

Cancer DWLOC for 3,5-DCA

Considerable degradation of vinclozolin and its metabolites to 3,5-DCA in the soil/water column is likely to occur over time. Therefore, it is a conservative yet reasonable assumption that the highest chronic EEC level (3.12 ppb in surface water) occurs in drinking water. The carcinogenic DWLOC for 3,5-DCA has been calculated to be 0.25 ppb for the general population; the EEC exceeds the DWLOC by 12x indicating a potential for concern. Note, however, that this estimate is based on a model that assumes 100% degradation to 3,5-DCA in soil and water and that the dietary portion of the calculation assumes a worst-case estimate of the proportion of the total residue 3,5-DCA comprises (10% of the total radioactive residue) in plant metabolism studies.

RESIDENTIAL EXPOSURE AND RISK ASSESSMENT

There are no products containing vinclozolin that are available for sale to homeowners. Therefore, the Agency did not consider handler exposures for the general population (i.e., referred to as homeowner handler exposures). Vinclozolin can, however, be occupationally used in a manner that may lead to exposures to the general population including golfers on treated courses and homeowners and their families resulting from sodfarm use when treated sod is placed in a residential environment. A chemical-specific turf exposure study is available that measured human exposure as well as residue dissipation over time. All of the residential exposures are considered to be short-/intermediate-term duration for the purposes of this risk assessment (i.e., 1 day to 1 week and 1 week to several months, respectively). The same toxicological endpoints apply to both durations of exposure. In addition, since each of the exposure scenarios considered in the assessment occur at least sporadically, this places them in the short-term duration exposure category. In this assessment, separate toxicological endpoints/effects were identified for adult female populations and children (i.e., infants and toddlers). Endpoints were also identified that apply to different durations of exposure. Refer to Table 2 for a summary of the toxicity studies and the dose/toxic effects selected for risk assessment purposes. For adults (females 13+ are the target population), noncancer risk assessments were completed for short-/intermediate-term exposures using an oral NOAEL of 3 mg/kg/day. For children, an oral NOAEL of 5 mg/kg/day was used for short-/intermediate-term assessments. As both of these endpoints were derived from oral toxicity studies, route-to-route extrapolation has been performed, i.e., exposure has been corrected by applying the dermal absorption factor of 25% (based on a rat study) or the default inhalation absorption factor of 100%. The Agency level of concern is established during the risk assessment process using uncertainty factors for MOE calculations. For the residential risk assessments, an uncertainty factor of 100 has been used to account for interspecies extrapolation and intraspecies variability. Also, the FQPA safety factor was retained and has been applied in addition to the 100, bringing the Agency's level of concern to 1000 for these scenarios. Body weights of 15 and 60 kg have been used for toddler and adult risk calculations, respectively. The only exposure of children considered in this assessment is that related to the use of vinclozolin on sodfarms; exposure of toddlers was considered when defining the time required for vinclozolin residues to dissipate prior to the harvest of treated sod and placement into a residential setting.

Postapplication risks to the general population were only considered for golfers following treatment

of greens and tees and for toddlers resulting from vinclozolin use on sod farms. All of these exposures are considered to be of a short-/intermediate-term nature by the Agency. Adult golfer exposures were less than the Agency's level of concern (i.e., the uncertainty factor of 1000 was easily exceeded) even on the day of application (MOE = 6800). Likewise, given the magnitude of the MOE for adults, the Agency does not believe that risks for child golfers would exceed the level of concern. This lack of concern for golfers is expected considering that only tees and greens are treated and that golfers are basically walking on the treated turf. The aggregate MOE for toddlers playing on sodfarm turf (which represents an upper-bound exposure that includes dermal and nondietary ingestion pathways) is 33 on the day of application. Foliar dislodgeable residues on the sod decline such that risks don't fall beneath the Agency's level of concern until 24 days after application (MOE = 1096). A reentry interval or its equivalent is not considered appropriate for transplanted sod in a residential environment. Therefore, this 24-day residue dissipation period must occur prior to laying the sod, perhaps by the use of a required interval between the final treatment and cutting of the sod. If 2 days are allowed for sod harvest, transit, and placement, then treated sod cannot be harvested for at least 22 days after application.

This assessment reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines (7/24/97 Version)*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment (12/11/97 Version)*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential ExposureAssessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available and it is feasible from a regulatory perspective. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farmworker children; and exposures to children in schools.

AGGREGATE EXPOSURE AND RISK ASSESSMENT

Acute Aggregate Exposure and Risk

Acute aggregate risk exceeds the Agency's level of concern based on food sources of exposure alone. As a result, a DWLOC cannot be calculated. Acute dietary (food only) risks exceed the Agency's level of concern as the only applicable population, females 13-50, has a risk that is 210% of the aPAD (Table 3) based on moderately refined exposure estimates. However, to determine the potential relative magnitude residues in drinking water may contribute to the aggregate risk, it was assumed that all of the water consumed per day contains vinclozolin per se at the peak surface water EEC level; when this was done, the %aPAD consumed was minimal (females 13-50). If the total residue expressed as 3,5-DCA is assumed (see Table 5), then the percent of the aPAD

utilized would be somewhat higher yet still very low. Monitoring data could permit refinement of vinclozolin exposure through drinking water but it appears that food sources of dietary risk are the more significant contributors.

Aggregate Short-term and Intermediate-term Exposure and Risk

Short-term and intermediate-term aggregate risks have not been calculated because the residential component alone exceeds the Agency's level of concern. In addition, food and drinking water sources of exposure would also contribute to these aggregate risks. Risk mitigation options must be considered by vinclozolin stakeholders to determine the duration of the PHI necessary for treated sod to reduce residential risks to toddlers below the Agency's level of concern. Applying worst-case assumptions, the relative magnitude of the short-term/intermediate-term aggregate risk contributed by residues in food and drinking water is likely to be very small compared to that contributed by the residential sod exposure.

Chronic Aggregate Exposure and Risk

Chronic (noncancer) aggregate risk was below the Agency's level of concern for food and drinking water sources of exposure. Chronic food-source risks were $\leq$14% of the cPAD. Estimated Environmental Concentrations (EECs) were compared to the chronic DWLOCs. The chronic EEC for residues of vinclozolin per se in groundwater (0.53 ppb) was well below the chronic DWLOCs for water consumption by both adults (39 for the general population and 34 for females 13-50) and children (10 ppb). Even the much more conservative EEC for combined vinclozolin residues in surface water (3.12 ppb; see Table 5) is less than the chonic DWLOCs.

Carcinogenic Aggregate Exposure and Risk for Vinclozolin

Carcinogenic aggregate risk exceeded the Agency's level of concern (1×10^{-6}) as the associated risks were $1.3\text{-}2.5 \times 10^{-5}$ depending on which combination of proposed (canola and succulent bean) and cancelled (strawberry and stone fruit) uses are included in the assessment. As a result, DWLOCs (Q_1^* approach) were not calculated for vinclozolin and its metabolites. As an acceptable level of concern has not been determined for cancer risk using the nonlinear (MOE) approach, DWLOCs cannot be calculated for this type of assessment. However, using worst-case assumptions, carcinogenic dietary risk due to drinking water exposure could be of a magnitude similar to that contributed by food sources.

Carcinogenic Aggregate Exposure and Risk for 3,5-DCA

The dietary (food and wine only) cancer risk to the general population associated with 3,5-DCA derived from vinclozolin is estimated to be 5.43×10^{-7} (including stone fruit, strawberries, canola, and succulent beans) or 2.9×10^{-7} excluding strawberries and stone fruit. The DWLOC for 3,5-DCA

originating from vinclozolin has been calculated to be 0.25 ppb for the general population; the EEC exceeds the DWLOC by 12x indicating a potential for concern. Note, however, that this estimate is based on a model that assumes 100% degradation to 3,5-DCA and that the dietary portion of the calculation assumes a worst-case estimate of the proportion of the total residue 3,5-DCA comprises (10% of the total radioactive residue) in plant metabolism studies.

OCCUPATIONAL EXPOSURE AND RISK ASSESSMENT

Incident Data Review

Vinclozolin human incident data were reviewed 1/3/96 by V. Dobozy of HED. No incidents were reported involving vinclozolin by OPP's Incident Data System between 1992 and 1996, the Poison Control Centers from 1985 to 1992 DCI only involved organophosphates and carbamates), and the National Pesticide Telecommunications Network from 1984 to 1991. The California Department of Food and Agriculture, now the Department of Pesticide Regulation, reported three incidents of skin effects, one each in 1983, 1985, and 1989. The conclusion was that, due to the few reported incidents HED has no significant concerns or mitigating measures concerning acute poisoning incidents. Note, however, that the principle effects of vinclozolin are associated with the developmental effects afforded by its antiandrogenic activity.

A 12/22/99 epidemiology report by R. Allen of HED details studies of male workers in German vinclozolin production and formulation plants. The epidemiological study was reportedly well conducted. The study authors conclude that: "no antiandrogenic effects were found" and "there was no evidence of hormonal imbalance, prostate and liver effects, no toxic effects on lenses and no haemolytic anaemia among exposed employees." The study authors also report that the mean urine levels (apparently of 3,5-DCA-containing residues) of the 67 participants ranged from 70-1400 ug/L and "66% of the participants exceeded the 260 ug/L acceptable daily intake (ADI) for vinclozolin." The basis and origin of the ADI was not identified. There was a greater incidence of sexual potency disturbances and testicular abnormalities among controls than among study group subjects. Again, the principle effects of vinclozolin are developmental and reproductive and would not be expected to be detected in exposed adult workers.

OCCUPATIONAL EXPOSURE AND RISK

Vinclozolin is a fungicide used in agriculture on field crops, orchard crops, and small fruits. Vinclozolin may also be used in the ornamental/floriculture industry on woody and herbaceous ornamentals as a post-harvest cut flower dip or foliar spray, as a dip for nurserystock (e.g., bulbs, corms, budwood, and bare-root nursery stock), and on turf (golf courses on tees/greens and on sod farms). Vinclozolin can be applied using a wide array of application equipment. In agriculture, groundboom, aerial, and airblast applications can be made. Other applications are completed using handheld equipment such as low pressure handwand sprayers, backpack sprayers, low

pressure/high volume turfguns, and dipping tanks.

Occupational exposures can occur during the application process in agriculture and in the ornamental/floriculture market (i.e., referred to as handler exposures). These exposures involve individuals who complete all aspects of the application process including those who mix spray solutions (i.e., mixer/loaders), those who actually make the application (i.e., applicators), and those who direct aircraft while making aerial applications (i.e., flaggers). Occupational exposures can also occur as a result of entering previously treated areas to complete a task (i.e., referred to as postapplication exposures) such as harvesting, scouting, or maintenance/cultural activities. There is an extensive chemical-specific exposure database for vinclozolin that includes two handler exposure studies and nine postapplication studies on peaches, strawberries, and turf that measured human exposure as well as residue dissipation over time. Each of these studies has been used as appropriate in the development of this assessment. A variety of risk assessments have also been developed and submitted to the Agency by BASF Corporation, the producer and registrant, that have been considered in this document. All of the occupational exposures are considered to be short-/intermediate-term duration for the purposes of this risk assessment (i.e., 1 day up to 1 week and thereafter up to 180 days, respectively) as the same toxicological endpoint applies to both durations of exposure. In addition, since each of the exposure scenarios considered in the assessment occur at least sporadically, this places them in the short-term duration exposure category. In very limited cases, exposures can also occur over extended periods of time that are considered to be chronic in nature (i.e., 180 working days or more per year) or of sufficient duration for the development of cancer. These extended exposures are only thought to occur in the ornamental/floriculture market and are not in agriculture.

Occupational exposure endpoints were identified that apply to different durations of exposure as well as to the development of cancer and other noncancer effects (Table 2). For occupational short-/intermediate-term dermal and inhalation exposures, females 13+ are the target population; an oral NOAEL of 3 mg/kg/day was selected. In the case of occupational chronic noncancer assessments, an oral NOAEL of 1.2 mg/kg/day has been used to assess risk to the general population. Cancer risk calculations have also been completed in this assessment using a point of departure of 4.9 mg/kg/day using a threshold approach (i.e., cancer MOEs have been calculated) and a linear, low-dose extrapolation approach using a Q_1^* of 2.9×10^{-1} $(mg/kg/day)^{-1}$. The available mechanistic data indicate that cancers will develop only after exposures of an extended duration so these calculations were completed for a very limited number of scenarios where exposures of an extended duration are expected to occur. The level of concern to the Agency is established during the risk assessment process using uncertainty factors for MOE calculations and a quantitative population risk value for calculations using linear, low dose extrapolation. For the chronic, noncancer occupational risk assessments, an uncertainty factor of 100 is used to account for interspecies extrapolation and intraspecies variability. The Agency has not established a policy for defining uncertainty factors for cancer threshold calculations to date so these values are presented in the risk assessment for characterization purposes. The Agency has established a level of concern for cancer risks of $1x10^{-6}$ when the linear, low-dose extrapolation method is used. A cancer risk value of $1x10^{-4}$ can be used if efforts are made in occupational settings to further

mitigate risks. A dermal absorption factor of 25%, an inhalation absorption factor of 100%, and body weights of either 60 kg (females 13+ for short-/intermediate-term assessments) and 70 kg (representative of the general population for chronic and cancer assessments) have been used for all occupational risk calculations.

Occupational Handler Exposure and Risk

Based on the assessment of various exposure scenarios, the Agency has some risk concerns over the use of vinclozolin in both the agricultural and ornamental/floriculture marketplaces. When **short-/intermediate-term occupational exposures** are considered for handlers, risks associated with all of the exposure scenarios do not exceed the Agency's level of concern either in the agricultural or ornamental/floriculture marketplace; MOEs range from just over 100 to >10,000 depending upon the use scenario and level of personal protection (Table 6). This result is based on requiring different levels of personal protection for each exposure scenario considered. Some low use/low exposure scenarios do not exceed the Agency's level of concern at the baseline level of personal protection which entails the use of normal work clothing represented by long pants and a long-sleeved shirt (e.g., mixing/loading granules for airblast application to raspberries). In other cases, however, more extensive personal protection is required such as the use of gloves, additional PPE, respirators, or engineering controls such as closed tractor cabs or water soluble packaging for solid formulations.

Chronic or long-term occupational handler exposure scenarios were only considered for a very limited number of uses that are allowable in the ornamental/floriculture marketplace (e.g., foliar spray applied to cut flowers such as roses prior to storage/shipment). The risks in all of these exposure scenarios (Table 6) do not exceed the Agency's level of concern if chemical-resistant gloves are worn in addition to long pants and long-sleeved shirts during the application process (MOEs range from 210 to >10,000).

For all occupational handler scenarios considered in the **cancer risk assessment** (Table 6), MOEs ranged from approximately 20 to approximately 60,000 at the baseline level of personal protection (i.e., long-sleeved shirts and long-pants only). At the most appropriate maximum levels of personal protection (i.e., engineering controls or double layer clothing, gloves, and respirator -- depending upon scenario), MOEs ranged from approximately 1400 to 5900 for the handheld application methods and from approximately 100,000 to 2.9M when water soluble packaging was considered for preparing dipping solutions. Population-based cancer risk

Table 6. Occupational Handlers Summary of Risks (MOEs).

	Margin of Exposure[a]
Level of Protection	

	Short-/Intermediate-term	Chronic	Cancer (nonlinear)
Baseline	Of 55 scenario/crop combinations, 38 had MOEs >100; remaining 17 MOEs were 0.5-98	Of 4 chronic subscenarios, 2 MOEs were <100: 77 for FlC M/L for dipping cut flowers and 5.5 for M/L/A liquids with low-pressure handwand for spraying cut flowers	Of 4 subscenarios, MOEs were 23, 310, 13,000, and 60,000
Minimum PPE (gloves and PF 5 respirator)	Of 58 subscenarios, 50 MOEs were >100; other 8 were 22-85	Of 5 chronic subscenarios, all MOEs were >100	Of 5 chronic subscenarios, MOEs were 890-110,000
Maximum PPE (gloves and PF 10 respirator)	Of 58 subscenarios, 52 MOEs were >100; other 6 were 30-85	NA[b]	Of 5 chronic subscenarios, MOEs were 1,400-220,000
Engineering Controls	Of 52 subscenarios, all MOEs were >100	NA	Of 3 chronic subscenarios, MOEs were 100,000-3 x 10^6

[a]Subscenario = Scenario/crop combination.
[b]NA = Not applicable as the risk was below the Agency's level of concern at a lower level of protection.

Table 7. Occupational Cancer Assessment (linear low-dose extrapolation).

Scenario/crop[a]	90 Annual Exposure Days			180 Annual Exposure Days		
	Baseline	Double layer, gloves, no respirator	Engineering controls	Baseline	Double Layer, gloves, no respirator	Engineering controls
Mixing/loading dry flowable for dipping cut flowers, etc.	1.3×10^{-5}	9.7×10^{-6}	2.6×10^{-7}	2.7×10^{-5}	1.9×10^{-5}	5.3×10^{-7}
Mixing/loading flowable concentrate/liquid for dipping ornamentals	5.6×10^{-4}	4.4×10^{-6}	1.7×10^{-6}	1.1×10^{-3}	8.8×10^{-6}	3.5×10^{-6}
Mixing/loading extruded granules for dipping cut flowers, etc.	2.9×10^{-6}	2.0×10^{-6}	5.9×10^{-8}	5.9×10^{-6}	3.9×10^{-6}	1.2×10^{-7}
Mixing/loading/applying liquids with low-pressure handwand for spraying cut flowers	7.7×10^{-3}	3.8×10^{-5}	NF[b]	1.6×10^{-2}	7.6×10^{-5}	NF
Mixing/loading/applying liquids with a backpack sprayer for spraying cut flowers	9.2×10^{-6}	1.3×10^{-4}	NF	1.8×10^{-5}	2.7×10^{-4}	NF

[a]Only these five scenario/crop combinations are considered of a sufficient duration of exposure to potentially result in cancer.
[b]NF = Engineering controls are not feasible for this scenario/crop combination.

estimates for all scenarios considered were less than $1x10^{-4}$ (indicating that the exposure did not exceed the Agency's level of

concern) and in many cases were less than $1x10^{-6}$ depending upon the level of personal protection upon which the assessment is based (Table 7). The only scenario for which cancer risks exceeded the Agency's level of concern at all levels of personal protection considered was for backpack sprayers when used to treat cut flowers with a foliar spray. This pattern was reflected in the results regardless of the annual exposure frequency considered in the assessment (i.e., a total of 90 days and a total of 180 days annual exposure were considered). The results of the risk assessment for handlers should be considered in the context that the vast majority of occupational vinclozolin handler exposures are thought to be of a short-/intermediate-term nature by the Agency. Therefore, it is believed that exposures do not exceed the Agency's level of concern for virtually any of the vinclozolin handler exposures.

Occupational Postapplication Exposure and Risk

Agricultural Uses. The majority of concerns that the Agency has over the use of vinclozolin stem from the occupational postapplication exposures considered in this assessment. Postapplication risks are mitigated by the Agency using an administrative mitigation measure which is referred to as the Restricted Entry Interval (REI) which represents the amount of time required for residues to dissipate in treated areas prior to beginning a job or task in that area such that the resulting exposures do not exceed the Agency's level of risk concern (e.g., an uncertainty factor of 100 for noncancer occupational risk assessments). For most of the uses in agriculture, postapplication risks do not exceed the Agency's level of concern within 30 days after application (Table 8). [Note: All risks in agriculture, which does not include ornamental/floriculture uses, are considered to be short-/intermediate-term in duration as with the agricultural handler scenarios.] For activities in low row crops such as scouting canola or lettuce the Agency believes that reentry into treated areas can occur (i.e., risks do not exceed the Agency's level of concern) 9 days after application. The Agency also believes that reentry can occur 21 days after application for activities such as harvesting lettuce, after 25 days for harvesting kiwi, and after 27 days for scouting and harvesting raspberries and low-growing snapbeans. The only occupational scenarios in agriculture where postapplication risks exceeded the Agency's level of concern for more than 30 days after application was for hand harvesting of onions and trellised snapbeans (38 days are required) which are believed by the Agency to be plausible, yet not a very common practice in agriculture.

Ornamental/Floriculture Uses. The occupational postapplication risks for the ornamental and floriculture marketplaces included a short-/intermediate-term, chronic, and cancer risk assessment. **Short-/intermediate-term exposure** calculations were completed for all scenarios while an assessment for chronic exposures and exposures of sufficient duration to cause cancer were only completed for a select number of scenarios (Table 8). When short-/intermediate-term exposures are considered, risks for most uses do not exceed the Agency's level of concern within 30 days after application. For example, the Agency believes that mowing and maintaining treated turf can occur on the same day as application. The Agency also

Table 8. Occupational Postapplication Risks and Restricted Entry Intervals.

Activity/crop	REI (days) at which MOE exceeds 100		Cancer (nonlinear) MOE at 50 days	Cancer risk (linear) at 50 days postapplication (49 days in one case)	
	Short-/intermediate term	Chronic		Low frequency	High frequency
Scouting canola, onions, lettuce	9	–[a]	–	–	–
Harvesting lettuce	21	–	–	–	–
Scouting/harvesting raspberries	27	–	–	–	–
Harvesting onions	39	–	–	–	–
Harvesting kiwi	25	–	–	–	–
Mowing turf	0	–	–	–	–
Sorting/packing ornamentals	21	31	1900	9.8×10^{-5} at 49-day REI	1.8×10^{-4}
Irrigating ornamentals	27	37	1200	1.5×10^{-4}	2.9×10^{-4}
Turf (sod) harvesting	5	–	–	–	–
Cutting flowers with standard TC[b]	39	48	480	3.6×10^{-4}	7.3×10^{-4}
Cutting flowers with literature TC	30	39	970	1.8×10^{-4}	3.6×10^{-4}

[a]The activity/crop combination (–) is only of a short-/intermediate-term duration, i.e., other assessments are not applicable.
[b]TC = Transfer Coefficient.

believes that reentry can occur 21 days after application for activities such as sorting and packing ornamentals in a greenhouse, after 27 days when irrigating ornamentals, and after 5 days for harvesting or placing sod. The only occupational scenario for which postapplication risks exceeded the Agency's level of concern for more than 30 days after application was for cutting flowers in a

greenhouse: for this scenario, 30 to 39 days were required for exposures not to exceed the Agency's level of concern. **Chronic exposures** were only considered for certain tasks associated with the production of ornamentals in a greenhouse. In all cases, the durations required for entry into a previously treated area was extended compared to the short-/intermediate-term assessment. When exposures are of a chronic duration, the Agency believes that reentry can occur 31 days after application for activities such as sorting and packing ornamentals in a greenhouse, after 37 days when irrigating ornamentals, and 39 to 48 days for cutting flowers in a greenhouse (Table 8). For the **postapplication cancer risk assessment**, a maximum of 50 days after application was considered because durations longer than 50 days far surpass any logical proposal for establishing a viable REI. Given this premise, population-based cancer risks still exceed the Agency's level of concern even at 50 days after application for all activities considered including sorting/packing, irrigation, and cutting flowers
(i.e., all risks were > $1x10^{-4}$ for all scenarios considered even 50 days after application). Likewise, when cancer MOE values were calculated 50 days after application, these values were all <2000 for the same scenarios (Table 8). As with the handler risks summarized above, the results of the risk assessment for postapplication workers in the ornamental/floriculture marketplace should be considered in the context that the vast majority of these exposures are thought to be of a short-/intermediate-term nature by the Agency. Therefore, it is believed that the results of the short-/intermediate-term risk assessment would be protective for mitigating most occupational postapplication risks.

ENDOCRINE DISRUPTER EFFECTS

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." Vinclozolin and certain of its metabolites are known to interfere with the endocrine system exerting their effects most dramatically during the developmental stages of animals ultimately resulting in reproductive effects. The toxic effects induced by vinclozolin are specifically related to its antiandrogenic activity and its ability to act as a competitive antagonist at the androgen receptor. Male fertility decrements resulting from androgen deprivation of several organs are some of the more sensitive hazard endpoints. Some effects on male fertility include reduced sperm count, decreased prostate weight, and delayed puberty. Reproductive effects (seen in testes, sperm, epididymes, and ovaries) were observed at one or more dose levels in the chronic studies used to establish the chronic RfD. Vinclozolin and/or its metabolites also cause Leydig cell (testicular) tumors in rats by a nongenotoxic mode of action. There is also evidence in the published literature that vinclozolin may affect the development and function of the neuroendocrine system

EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine

Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of vinclozolin and its end-use products for endocrine effects may be required.

CUMULATIVE EXPOSURE AND RISK

Vinclozolin is a member of the imide group of the dicarboximide class of fungicides, as are iprodione and procymidone. EPA has certain evidence that these compounds induce similar toxic effects but has not yet determined whether or not these compounds modulate androgens by a common mechanism. In fact, there is evidence that iprodione disrupts the endocrine system by inhibiting androgen synthesis rather than competing for the androgen receptor as vinclozolin does. Also, these three imides do not have any known metabolites/degradates in common with the possible exception of 3,5-DCA. In addition, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. For this assessment of vinclozolin and its antiandrogenic metabolites, therefore, EPA will not conduct a cumulative risk assessment.

The Agency will, however, consider the relative contribution of each of these related pesticides to the cumulative/multichemical and multiroute/aggregated carcinogenic dietary risk resulting from exposure to 3,5-DCA which is a metabolite common (to some extent) to all three compounds. The Q_1^* used for the 3,5-DCA cancer risk assessments is that of p-chloroaniline, a direct-acting carcinogen inducing spleen sarcomas. As 3,5-DCA has no known pesticidal, pharmaceutical, or cosmetic uses, there is no toxicity database for this chemical. As a result, no other toxic effects are known or suspected to be associated with 3,5-DCA.

Vinclozolin. As summarized above, the dietary (food and wine only) cancer risk to the general population associated with 3,5-DCA derived from vinclozolin is estimated to be 5.4×10^{-7} (including stone fruit, strawberries, canola, and succulent beans) or 2.9×10^{-7} excluding strawberries and stone fruit. This cancer risk due to food sources of exposure alone is below the Agency's level of concern ($<1 \times 10^{-6}$). The DWLOC for 3,5-DCA originating from vinclozolin has been calculated to be 0.25 ppb for the general population; the EEC exceeds the DWLOC by 12x indicating a potential for concern.

Iprodione. The risk associated with 3,5-DCA derived from iprodione, from the 7/31/98 RED by C. Scheltema (D233218), was 6×10^{-9} from food sources. The DWLOC for 3,5-DCA derived from domestic uses of iprodione was estimated to be 0.55 ppb. The 3,5-DCA EEC in surface water associated with the use of iprodione alone was estimated to be 0.45 ppb. Thus the iprodione-derived 3,5-DCA carcinogenic DWLOC is not exceeded.

Procymidone. The cancer risk associated with 3,5-DCA in imported wine produced from grapes treated with procymidone was estimated to be 3.7×10^{-7} (7/31/98 iprodione RED). There is no food or drinking water exposure because procymidone is not registered for use in the U.S.

The cumulative, food-only cancer risk associated with 3,5-DCA derived from all three of these imide fungicides is 9.2×10^{-7} if vinclozolin-treated stone fruits, strawberries, canola, and succulent beans are assumed to be available for consumption; cumulative food risks are 6.6×10^{-7} if stone fruits and strawberries are excluded. Both of these food-only risks are considered by the Agency to be negligible cancer risks. However, the EEC exceeds the carcinogenic DWLOC for 3,5-DCA originating from vinclozolin alone by a factor of 12x indicating a potential for concern. The iprodione-associated 3,5-DCA carcinogenic DWLOC is not exceeded; however, some dietary exposure to 3,5-DCA is expected from this source in addition to the food, wine, and vinclozolin-derived water sources identified above. These sources further increase the cumulative carcinogenic dietary risk associated with the various pesticidal sources of 3,5-DCA.

DATA NEEDS

Toxicology

870.6300 Developmental Neurotoxicity Study (DNT) is required because, based on published literature, exposure to vinclozolin *in utero* or during early development has the potential to affect the development and function of the neuroendocrine system. The Agency acknowledges that the current DNT protocol may not be sufficient to detect the subtle findings reported in the current literature. An expanded DNT study protocol may be necessary to assess the relevant endpoints.

Occupational and Residential Exposure

Data needs will be assessed during the risk mitigation process. Risks associated with certain occupational and residential exposures require mitigation.

Residue Chemistry

Although not required, the following data/information would permit dietary risk refinement:

- Monitoring data (market basket survey concentrating on single-serving samples for unblended commodities)
- Wine fermentation studies to determine degradation/metabolism during the fermentation process
- Cooking/canning data to determine any degradation associated with these processes
- Refined percent crop treated data for imported commodities including kiwi, endive, and perhaps others such as wine grapes

If BASF opts to perform any of the first three studies, it is recommended that agreement with the Agency be reached regarding protocols and analytes to be determined.

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